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MATHEWS, COLLINS, SHEPHERD & MCKAY, P.A.
100 THANET CIRCLE, SUITE 306
PRINCETON, NJ 08540-3674

EXAMINER	
LI, QIAN JANICE	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/845,938	KABANOV ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 January 2004* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29-40 and 70-77* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29-40 and 70-77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The response and amendment filed 1/12/04 have been entered. Claims 1-28, 41-69 have been canceled. Claims 29-40 and 70-77 are under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims will not be reiterated. The arguments in 1/12/04 response would be addressed to the extent that they apply to current rejection.

Claim Rejections

Claims 35, 37, 40 are newly objected to because "thereof" should be deleted in the phrase "polynucleotide derivative thereof".

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 29-40 and 70-77 are newly rejected under 35U.S.C. 112 first paragraph, because the specification as originally filed does not describe the invention as now claimed. The original disclosure fails to specify the term "non-modified polyoxyethylene-polyoxypropylene" as now claimed. The term is thus considered to be new matter.

MPEP 2163.02 teaches that "WHENEVER THE ISSUE ARISES, THE FUNDAMENTAL FACTUAL INQUIRY IS WHETHER A CLAIM DEFINES AN INVENTION THAT IS CLEARLY CONVEYED TO

THOSE SKILLED IN THE ART AT THE TIME THE APPLICATION WAS FILED...IF A CLAIM IS AMENDED TO INCLUDE SUBJECT MATTER, LIMITATIONS, OR TERMINOLOGY NOT PRESENT IN THE APPLICATION AS FILED, INVOLVING A DEPARTURE FROM, ADDITION TO, OR DELETION FROM THE DISCLOSURE OF THE APPLICATION AS FILED, THE EXAMINER SHOULD CONCLUDE THAT THE CLAIMED SUBJECT MATTER IS NOT DESCRIBED IN THAT APPLICATION". MPEP 2163.06 further notes "WHEN AN AMENDMENT IS FILED IN REPLY TO AN OBJECTION OR REJECTION BASED ON 35 U.S.C. 112, FIRST PARAGRAPH, A STUDY OF THE ENTIRE APPLICATION IS OFTEN NECESSARY TO DETERMINE WHETHER OR NOT "NEW MATTER" IS INVOLVED. *APPLICANT SHOULD THEREFORE SPECIFICALLY POINT OUT THE SUPPORT* FOR ANY AMENDMENTS MADE TO THE DISCLOSURE" (emphasis added). In the instant case, the specification as originally filed does not recite or define the term "non-modified", and the response filed with the amendment fails to specifically point out where in the specification the support for the amendment could be found. Thus, it is determined that the amendment is a departure from or an addition to the disclosure of the application as filed, accordingly, it introduces new matter into the disclosure.

To the extent that the claimed methods are not described in the instant disclosure, claims 29-40 and 70-77 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described.

For reasons set forth above, the amendment filed 1/12/04 is objected to under 35 U.S.C. §132 because it introduces new matter into the disclosure. 35 U.S.C. §132 states that no amendment shall introduce new matter into the disclosure of the

invention. Applicant is required to cancel the new matter in the reply to this Office Action.

Claims 29-40 and 70-77 are newly rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The methodology for determining adequacy of Written Description to convey that applicant was in possession of the claimed invention includes determining whether the application describes an actual reduction to practice, determining whether the invention is complete as evidenced by drawings or determining whether the invention has been set forth in terms of distinguishing identifying characteristics as evidenced by other descriptions of the invention that are sufficiently detailed to show that applicant was in possession of the claimed invention (*Guidelines for Examination of Patent Applications under 35 U.S.C. § 112, p 1 "Written Description" Requirement;* Federal Register/ Vol 66. No. 4, Friday, January 5, 2001; II Methodology for Determining Adequacy of Written Description (3.)).

Claims recite, "polynucleotide or *derivative thereof*". The specification fails to define the term derivative, given the plain meaning of "derivative", it encompasses any substance derived or obtained from a polynucleotide, and containing essential elements of a polynucleotide, or any compound that is not radical, original, or fundamental; originating, deduced, or formed from a polynucleotide; or a compound that is secondary

to a polynucleotide. Given the broadest reasonable interpretation, the claims encompass numerous chemicals that may induce or are inert in inducing an immune response. In view of the guidance provided in the specification, other than a polynucleotide vector encoding an antigenic protein, the specification fails to teach any polynucleotide derivatives that could induce an immune response or activate dendritic cells. Accordingly, the specification fails to provide an adequate description for the derivatives of a polynucleotide, particularly in their ability in inducing immune response.

An adequate written description for a derivative of a polynucleotide requires more than a mere statement that it is part of the invention, what is required is its chemical structure or sequence. The court has made it very clear "CONCEPTION OF CHEMICAL COMPOUND REQUIRES THAT INVENTOR BE ABLE TO DEFINE COMPOUND SO AS TO DISTINGUISH IT FROM OTHER MATERIALS, AND TO DESCRIBE HOW TO OBTAIN IT, RATHER THAN SIMPLY DEFINING IT SOLELY BY ITS PRINCIPAL BIOLOGICAL ACTIVITY". *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

To the extent that the claimed methods are not adequately described in the instant disclosure, claims 29-40 and 70-77 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since from the disclosure, the skilled artisan could not envision the detailed structure of the derivative, thus, would not know how to use the derivative.

Claims 29-40 and 70-77 are newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for increasing an immune response or activation of dendritic cells comprising administering to a mammal a composition comprising a polynucleotide encoding an antigen, does not reasonably provide enablement for doing so by administering any polynucleotide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention the invention commensurate in scope with these claims.

The factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention are summarized in *In re Wands*, (858 F2d 731, 737, 8 USPQ 2d 1400, 1404, (Fed Cir.1988)). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided. The factors most relevant to this rejection are the scope of the claims relative to the state of the art and the levels of the skilled in the art, and whether sufficient amount of direction or guidance are provided in the specification to enable one of skill in the art to practice the claimed invention.

Given the broadest reasonable interpretation, the claims encompass administering *any* polynucleotide and a polyoxyethylene-polyoxypropylene block copolymer to a mammal for inducing activation of dendritic cells or increasing an immune response, and doing so for therapeutic purpose. However, the specification

fails to teach that any polynucleotide combined with the block copolymer would induce an immune response. The specification teaches that cationic complexes of polynucleotide have been shown to *enhance* uptake and gene expression in virtually all tissue types *except* muscle, while non-ionic block copolymer could do so in intramuscular administration. In examples 60 and 61, the specification teaches intramuscular injection of a vector encoding and expressing a model antigen (beta-gal) as oppose to an empty vector formulated with block copolymers, isolating and culturing cells from the site of injection, and comparing the presence and amount of dendritic cells that may arise from such culture. The table in page 108 of the specification shows that neither the polynucleotide nor the block copolymer alone could lead to the growth of dendritic cells ex vivo, the polynucleotide encoding a model antigen plus the copolymers would lead to a significant growth of dendritic cells, and the combination of an empty vector and block copolymer would lead to a small number of dendritic cell growth. However, the specification fails to teach that such small number of dendritic cell growth (10% without an antigen vs. 90% with an antigen) would be therapeutically significant in terms of inducing or increasing an immune response to a desired level, and the specification fails to teach whether any other polynucleotide beyond a plasmid vector causes the possible activation of dendritic cells, and what are the polynucleotides. Thus, the specification fails to provide an enabling disclosure to support the full scope of the claims.

In view of the state of the art, it is well known in the art that administering a sufficient amount of polynucleotide encoding an antigen to a mammal could induce an

immune response to that antigen and causing the activation of dendritic cells such as taught by *Carson et al* (US 5,830,877, e.g. column 7, § t), and *Manthorpe et al* (US 2002/0,019,358, e.g. claim 40). However, it is unknown and the specification fails to teach that any polynucleotide would induce an immune response and activate dendritic cells, and the specification fails to teach what these polynucleotides are, thus, fails to provide an enabling disclosure for what is now claimed. In fact, US patent 6,656,459 shown that the claimed formulation would reduce rather than increase an immune response (e.g. the abstract). In view of such, the invention does not appear to be enabled in the absence of clarification of the contradictory evidence found in the reference.

Therefore, in view of the limited guidance, the lack of predictability of the art and the breadth of the claims, one skill in the art could not practice the invention without undue experimentation as it is broadly claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 29-40 and 70-77 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims are vague and indefinite because of the claim recitation, "non-modified polyoxyethylene-polyoxypropylene". The specification fails to define the term, it is

unclear what the term encompasses or excludes, and thus the metes and bounds of the claims are uncertain.

Claims are vague and indefinite because of the claim recitation, "polynucleotide or derivative thereof". The specification fails to define the term "derivative", given the plain meaning of "derivative", it encompasses any substance derived or obtained from another and containing essential elements of the parent substance, or any compound that is not radical, original, or fundamental; originating, deduced, or formed from something else; secondary to a polynucleotide. It is unclear what the phrase encompasses or excludes, or how to determine whether a compound is the derivative, thus the metes and bounds of the claims are unclear.

Claims 30, 33, 35, 38, 71 recite the limitation "the block copolymers". There is insufficient antecedent basis for this limitation in the claim.

Claim 77 is vague and indefinite because it recites, "improving the immune response", "improving" encompasses increase or decrease, or non-responsive (tolerant), it is unclear the meaning of the word in the context of the claim, thus the metes and bounds of the claims are uncertain.

Claim 77 is vague and indefinite because it recites "the composition according to claim 34, yet, claim 34 is a method claim. Thus the metes and bounds of the claims are unclear.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.
>
> (f) he did not himself invent the subject matter sought to be patented.

Claims 29-40 and 70-77 are rejected under 35 U.S.C. 102(e) as being anticipated by *Manthorpe et al* (US 2002/0,019,358).

Manthorpe et al teach a method comprising administering to a mammal a composition comprising a polynucleotide and an auxiliary agent that is a non-ionic polyoxyethylene-polyoxypropylene block copolymer comprises at least Pluronic F127 and L61 (claims 1, 28, 29, 38-40, and table V), wherein the composition could be administered via various routes such as intramuscular and subcutaneous routes (paragraph 0136) for inducing a desired immune response (claim 40). Accordingly, *Manthorpe et al* anticipate the instant claims.

Claims 29-40 and 70-77 are rejected under 35 U.S.C. 102(e) as being anticipated by *Kabanov et al* (US 6,387,406).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome

either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Kabanov et al teach a method comprising administering to a mammal a polyoxyethylene-polyoxypropylene block copolymer and a biologically active agent (claim 1), wherein the biologically active agent is a polynucleotide (column 7, lines 35 & 36), and wherein the block copolymer comprises at least Pluronic F127 and L61 (column 15, table). Although the means of administration is focused on oral delivery in the cited patent, they teach other means of administration such as intramuscular and intradermal routes, only these routes are not as convenient as oral route (column 1, lines 28-34). Accordingly, *Kabanov et al* anticipate the instant claims.

It is noted in this and the following rejections, the cited art does not recite inducing activation of dendritic cells, or increasing an immune response. However, the recitations only reflect the intended use of the method. Please note that intended use limitations bear little weight on the determination of novelty of the invention. This is because a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963). In the instant case, since the reference patent administering the same composition as claimed and using the same method steps, it would be able to perform the intended use, i.e. activation of dendritic cells or increasing an immune response. It is a general rule that merely discovering and claiming a new benefit to an old process cannot render the process again patentable. *In re Woodruff* 919 F. 2d 1575, 1577-78, 16 USPQ2d 1934, 1936-37 (Fed. Cir. 1990); *In re Swinehart*, 439 F. 2d 210, 213, 169 USPQ 226, 229 (CCPA 1971); and *Ex Parte Novitski*, 26 USPQ2d 1389, 1391 (Bd. Pat. App. & Int. 1993).

Claims 29-40 and 70-77 are rejected under 35 U.S.C. 102(e) as being anticipated by *Kabanov et al* (US 6,656,459).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Kabanov et al teach a method comprising administering to a mammal a composition comprising non-ionic polyoxyethylene-polyoxypropylene block copolymer and a biologically active agent, and wherein the non-ionic block copolymer comprises at least Pluronic F127 and L61 (claim 1 and abstract), wherein the composition may comprises polynucleotide (column 15, line 34), and wherein the composition could be administered via various routes such as intramuscular and intradermal routes (column 6, lines 59-67). Accordingly, *Kabanov et al* anticipate the instant claims.

Claims 29-40 and 70-77 are rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter. The cited US patents 6,387,406 and 6,656,459 anticipate these claims, but instant application has a different inventive entity. Hence, it is unclear who is the real inventor.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 29, 31, 32, 34, 36, 37, 39, 40, 70, 72, 74-77 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Raz et al* (US 6,589,940), in view of *Kabanov et al* (5,656,611, IDS), and evidenced by *Jakob et al* (J Immunol 1998;161:3042-9).

Raz et al teach administering to a subject a polynucleotide, e.g. an ISS-containing or CpG-containing oligodeoxynucleotides, preferably along with a block copolymer (column 17, line 27), and in the form of a colloidal dispersion (column 16, lines 55-59) for inducing an immune response. *Raz et al* do not specifically teach the polyoxyethylene-polyoxypropylene block copolymer or the state of the block copolymer.

Kabanov et al teach that block copolymer could increase the stability of a polynucleotide and increase the ability of nucleic acids to cross cell membranes and acting in the interior of a cell (abstract). *Kabanov et al* particularly teach the polyoxyethylene-polyoxypropylene block copolymer (e.g. columns 7 and 8), the state of the copolymer, and how to avoid gel formation of the composition (column 11). It is noteworthy *Kabanov et al* also teach the pluronic copolymer, a type of non-ionic polyoxyethylene-polyoxypropylene block copolymer (column ,)

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by *Raz et al* by simply using the copolymer as taught by *Kabanov et al* in the method of *Raz et al* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because the copolymer could enhance the cell entry, thus, the efficacy of the polynucleotide. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

The amended claims are drawn to using "non-modified polyoxyethylene-polyoxypropylene" block copolymer, since the specification fails to describe the term, this new limitation could not be assessed.

In the 1/12/04 response, Applicants argue that *Raz et al* does not contemplate, suggest, or describe polyoxyethylene-polyoxypropylene block co-polymers, and Kabanov et al stress the advantages of polycationic polyether block copolymers to increase the ability of crossing cell membranes, but fails to suggest or describe any method of inducing the activation of dendritic cells or modulating an immune response. Applicants further cited case law In re Rouffet to support the arguments.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, the Office does not simply cite two unrelated prior art, the nexus is present in both reference, *Raz et al* teach inducing an immune response with a

polynucleotide and a block copolymer for enhancing cell delivery of the polynucleotide, and *Kabanov et al* teach the art known block copolymers such as polyoxyethylene-polyoxypropylene having the function of stabilizing polynucleotide and promoting cell entry of a polynucleotide, thus, when the polynucleotide functions as inducing an immune response, the efficacy of its function would be enhanced. Since Kabanov et al teach various forms of block copolymer, it would have been obvious for one reasonably skilled to select one of the art known copolymers for the composition of *Raz et al.* Given the numerous block copolymers known in the art, this limitation would fall within the bound of optimization. Accordingly, it is the combined teachings of *Raz et al and Kabanove et al* that are obvious over the claimed invention. Moreover, even though *Raz et al and Kabanove et al* do not teach that the block copolymer could activate dendritic cells, it is a general rule that merely discovering and claiming a new benefit to an old process cannot render the process again patentable. *In re Woodruff* 919 F. 2d 1575, 1577-78, 16 USPQ2d 1934, 1936-37 (Fed. Cir. 1990); *In re Swinehart*, 439 F. 2d 210, 213, 169 USPQ 226, 229 (CCPA 1971); and *Ex Parte Novitski*, 26 USPQ2d 1389, 1391 (Bd. Pat. App. & Int. 1993). Accordingly, the rejection stands.

Applicants further argue that the polyoxyethylene-polyoxypropylene block copolymer as now presented do not increase the ability of nucleic acids to cross cell membranes (Specification, page 53), yet unexpectedly, activation of dendritic cells is induced as shown in pages 106-108 of the specification.

In response, the text in page 53 of the specification teaches that cationic complexes of polynucleotide have been shown to enhance uptake and gene expression

in virtually all tissue types *except* muscle, and non-ionic block copolymer could do so in intramuscular administration, however, the invention as claimed is not limited to intramascular administration nor cationic or nonionic complex polynucleotides, accordingly, the claimed invention stand obvious over the cited art. Further, the examples 60 and 61 of the specification fails to confirm that the dendritic cells are activated by the polyoxyethylene-polyoxypropylene block copolymers, because as shown in the table on page 108, example 61, the block copolymer alone or empty vector alone does not activate dendritic cells, it is only when both are present, dendritic cells could be activated at various degrees even by an empty vector. Here, apparently, the block copolymer did not activate dendritic cells, but the combination of the two did. Thus, it is improper to argue that the non-ionic copolymer activated dendritic cells. It appears that it only enhanced the efficacy of a polynucleotide in inducing an immune response as known in the art. Accordingly, for reasons of record and set forth above, the rejection stands.

Claims 29, 31, 32, 34, 36, 37, 39, 40, 69, 70, 72, 74-77 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Carson et al* (US 5,830,877), in view of *Kabanov et al* (5,656,611).

Carson et al teach a method for inducing immune response to an antigen comprising delivering a polynucleotide encoding the antigen to a host cell (column 7, lines 29-45) by intradermal or intramuscular injection of the polynucleotide. *Carson et al* also teach using cationic liposome to enhance gene delivery (column 3, lines 24-25).

They go on to teach that the Th1 response induced by the polynucleotide is the result of antigen activation of antigen-presenting cells such as dendritic cells (column 7, § t.). *Carson et al* do not specifically teach the polyoxyethylene-polyoxypropylene block copolymer or the state of the block copolymer, but this was taught by *Kabanov et al* as discussed above.

The amended claims are drawn to using "non-modified polyoxyethylene-polyoxypropylene" block copolymer, since the specification fails to describe the term, this new limitation could not be assessed.

Applicants argue that this rejection has the same fundamental legal weakness as in the combination of Raz and Kabanov. And further argue that both Carson and Kabanov stress and teach toward cationic entities to affect the efficacy of nucleic acid.

In response, with respect to the allegation of legal weakness, the argument has been addressed in the immediate preceding rejection, and thus would not be reiterated here. With respect to the type of polyoxyethylene-polyoxypropylene block copolymers, it is noted that *Carson et al* do teach using detergents to facilitate the delivery of polynucleotide, which is an art-known form of nonionic block copolymer. *Kabanov et al* also teach the pluronic copolymer, a type of non-ionic polyoxyethylene-polyoxypropylene block copolymer.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by *Carson et al* by simply using the copolymer as taught by *Kabanov et al* in the method of *Carson et al* with a reasonable expectation of success. The ordinary skilled artisan would have been

motivated to modify the claimed invention because the copolymer could enhance the cell entry, thus the efficacy, of the polynucleotide, subsequently, an immune response would be enhanced if the polynucleotide functions as inducing immune response. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 30, 33, 35, 38, 71, and 73 stand rejected and the rejection has been modified under 35 U.S.C. 103(a) as being unpatentable over *Raz et al* (US 6,589,940) or *Carson et al* (US 5,830,877), and *Kabanov et al* (5,656,611) as applied to claims 29, 31, 32, 34, 36, 37, 39, 40, 69, 70, 72, and 74-77 above, further in view of *Alakhov et al* (6,218,438) or *Kabanov et al* (6,387,406), or *Manthorpe et al* (US 2002/0,019,358).

The combined teachings of *Raz et al or Carson et al, and Kabanov et al* do not particularly teach a block copolymer comprising at least Pluronic F127 and L61. However, before the effective filing date of the instant invention, *Alakhov et al* teach that the block copolymers could be formulated with a biological agent comprising Pluronic F127 and L61 (Tabs 5 & 9).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by *Raz et al* or *Carson et al and Kabanov et al* by simply using the specific Pluronic F127 and L61 copolymer as taught by *Alakhov et al* in the method of *Raz et al* or *Carson et al* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because it is within the bound of optimization of a

copolymer formulation. Thus, the claimed invention as a whole was clearly *prima facie* obvious in the absence of evidence to the contrary.

The amended claims are drawn to using "non-modified polyoxyethylene-polyoxypropylene" block copolymer, since the specification fails to describe the term, this new limitation could not be assessed.

Applicants argue that this rejection has the same fundamental legal weakness as in the combination of *Raz* and *Kabanov* or *Carson* and *Alakhov*. And further argue that Kabanov 438 formulation comprises metal and metal-chelating agents, and does not teach formulations for the administration of nucleic acids or the activation of dendritic cells.

In response, with respect to the allegation of legal weakness, the argument has been addressed above, and thus would not be reiterated here. With respect to the type of polyoxyethylene-polyoxypropylene block copolymers, it is noted that *Carson et al* do teach using detergents to facilitate the delivery of polynucleotide, which is an art-known form of nonionic block copolymer. *Kabanov et al* also teach the pluronic copolymer, a type of non-ionic polyoxyethylene-polyoxypropylene block copolymer, the *Alakhov* patent is relied on for particular formulations of a nonionic non-ionic polyoxyethylene-polyoxypropylene block copolymer, even though it does not particularly teach delivering a polynucleotide, in the absence of evidence to the contrary, the different nonionic block copolymers should have similar physiological properties in polynucleotide stability and delivery. Accordingly, this limitation falls within the bound of optimization. It is noted that obviousness does not require absolute predictability of success; for obviousness under

35 U.S.C. § 103, all that is required is a reasonable expectation of success. See In re O'Farrell, 7 USPQ2d 1673 (CAFC 1988).

Moreover, the amended rejection include two new references indicating that the reasonably skilled in the art would know to use a formulation comprising at least Pluronic F127 and L61 copolymers in a polynucleotide delivery composition. Accordingly, the claimed invention as a whole was *prima facie* obvious.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 29-40 and 70-77 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 2, 3, 13, 18, 21, and 23 of U.S. Patent No. 6,359,054.

Applicants request to defer resolution of this rejection until a later time and acknowledged the willingness to file a terminal disclaimer if necessary.

Until then, for reasons of record, the rejection stands.

Claims 29-40 and 70-77 are newly rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 9, 10 of U.S. Patent No. 6,387,406.

Although the conflicting claims are not identical, they are not patentably distinct from each other because instant claims and claims of the cited patent are each drawn to a method comprising a polynucleotide or derivative thereof and at least one polyoxyethylene-polyoxypropylene block copolymer parenterally or intramuscularly in amounts insufficient for gel formation, wherein the composition comprising Pluronic L61 and F127, and forms aqueous dispersion.

Instant claims differ from claims of the cited patent in that the instant claims recite "inducing activation of dendritic cells" in the preamble, whereas claims of the cited patent recite "treating a mammal". However, because the claimed method comprises the same method steps, administering substantially identical compositions, the method in the cited patent would perform the function of activating dendritic cells.

Accordingly, the claimed processes in the copending and the present application are obvious variants. Inventions as claimed are co-extensive.

Claims 29-40 and 70-77 are newly rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 8-14 of U.S. Patent No. 6,656,459.

Although the conflicting claims are not identical, they are not patentably distinct from each other because instant claims and claims of the cited patent are each drawn to a method comprising a polynucleotide or derivative thereof and at least one polyoxyethylene-polyoxypropylene block copolymer parenterally or intramuscularly in amounts insufficient for gel formation, wherein the composition comprising Pluronic L61 and F127, and forms aqueous dispersion.

Instant claims differ from claims of the cited patent in that the instant claims recite "inducing activation of dendritic cells" in the preamble, whereas claims of the cited patent recite "for reducing inflammation". However, because the claimed method comprises the same method steps, administering substantially identical compositions, the method in the cited patent would perform the function of activating dendritic cells.

Accordingly, the claimed processes in the copending and the present application are obvious variants. Inventions as claimed are co-extensive.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is 571-272-0730. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Amy Nelson** can be reached on 571-272-0804. The fax numbers for the organization where this application or proceeding is assigned are **703-872-9306**.

Any inquiry of formal matters can be directed to the patent analyst, **Dianiece Jacobs**, whose telephone number is (571) 272-0532.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is **703-308-0196**.

JANICE LI
PATENT EXAMINER

Q. Janice Li
Patent Examiner
Art Unit 1632

QL
March 19, 2004